mTOR Inhibitors: Past, Present and Future

Moderator: Elizabeth Skufca

Presenters: David Ritter, MD, PhD and Michael Wong, MD, PhD

June 30, 2026

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Elizabeth Skufca

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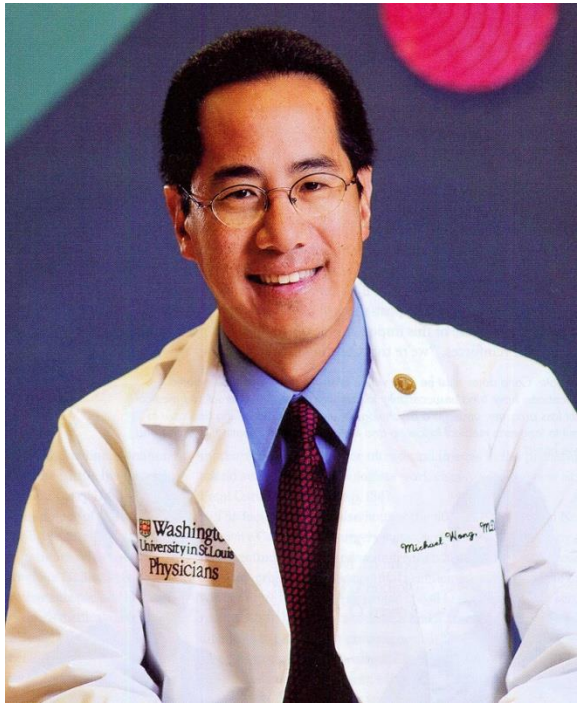
Today’s presenters

David Ritter, MD, PhD



Michael Wong, MD, PhD

Outline

Past

- Discovery of rapamycin and the TSC-mTOR pathway

Present

- Treatment of tumors in TSC with mTOR inhibitors
- Treatment of epilepsy and neurological symptoms in TSC
- Side effects of mTOR inhibitors

Future

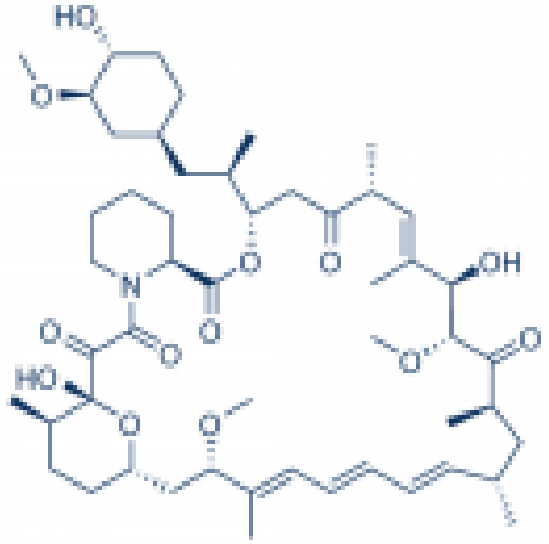
- Potential new treatment directions for mTOR inhibitors

Past

Discovery of rapamycin and the TSC-mTOR pathway

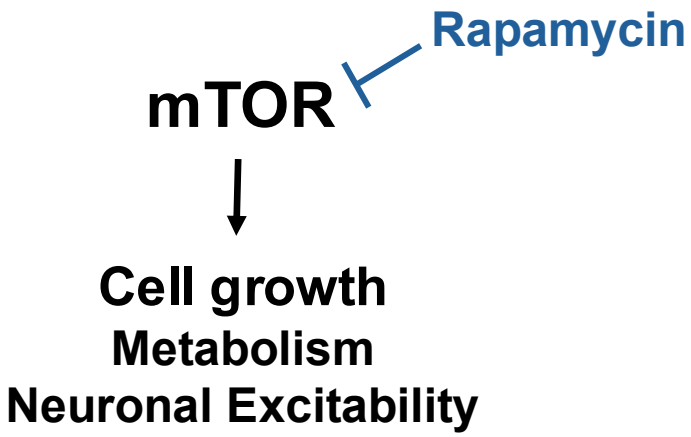
Discovery of Rapamycin

Rapa Nui

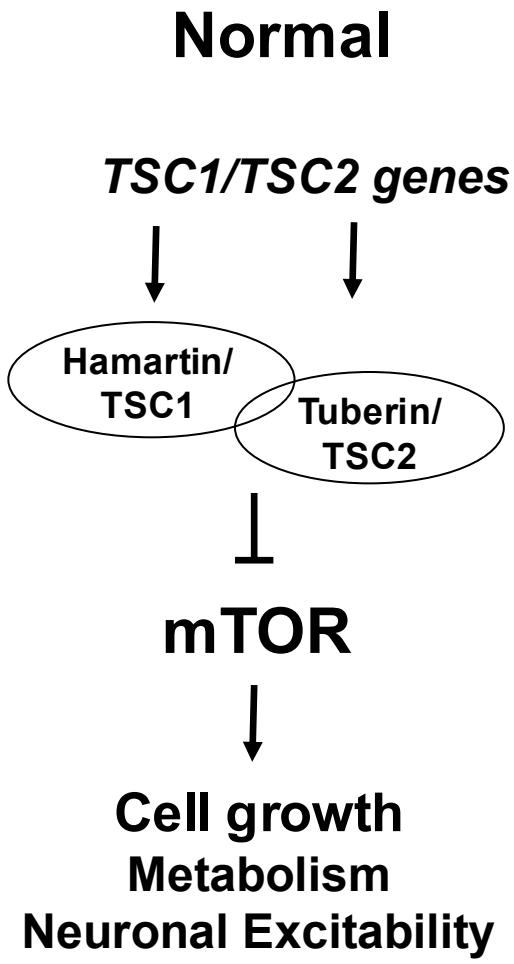


Rapamycin

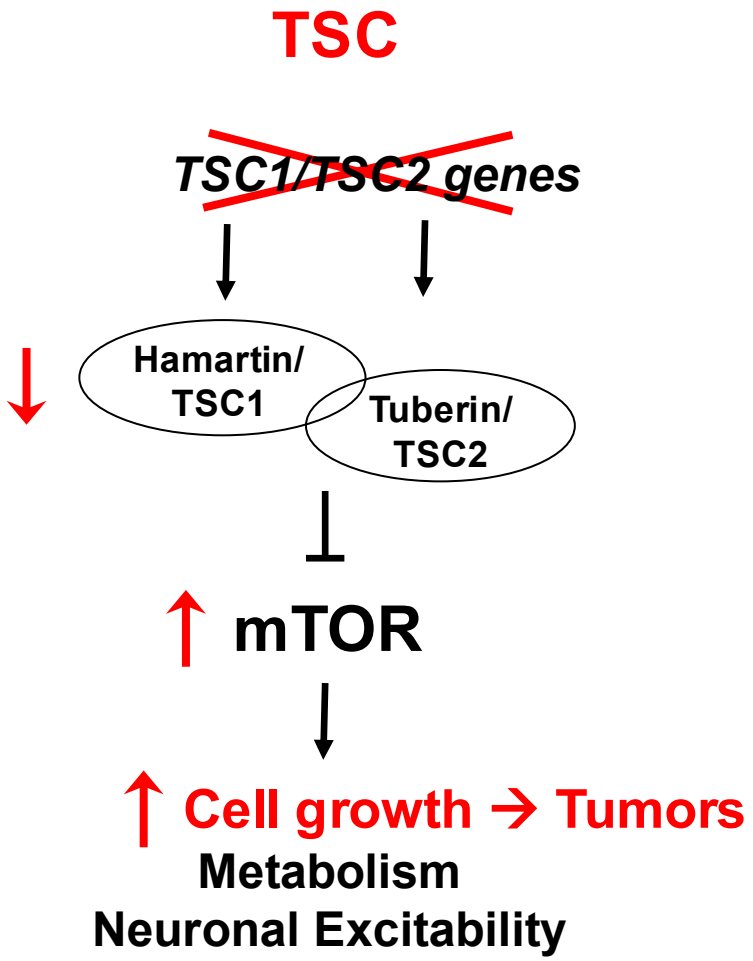
The TSC genes and the mTOR pathway



The TSC genes and the mTOR pathway



The TSC genes and the mTOR pathway



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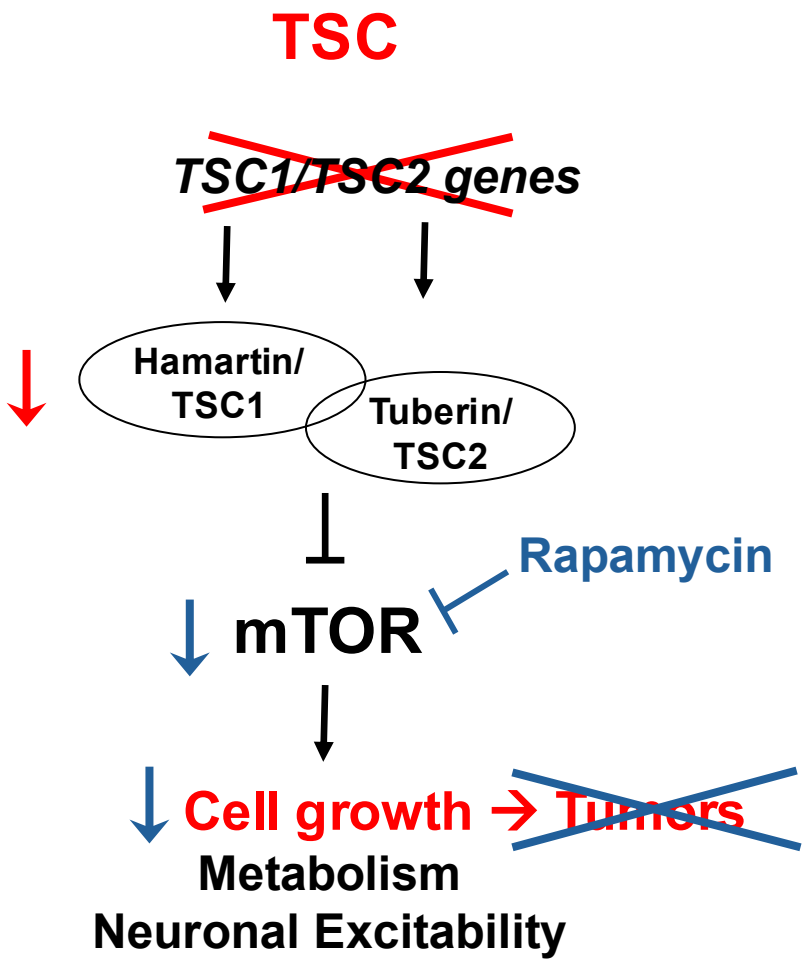

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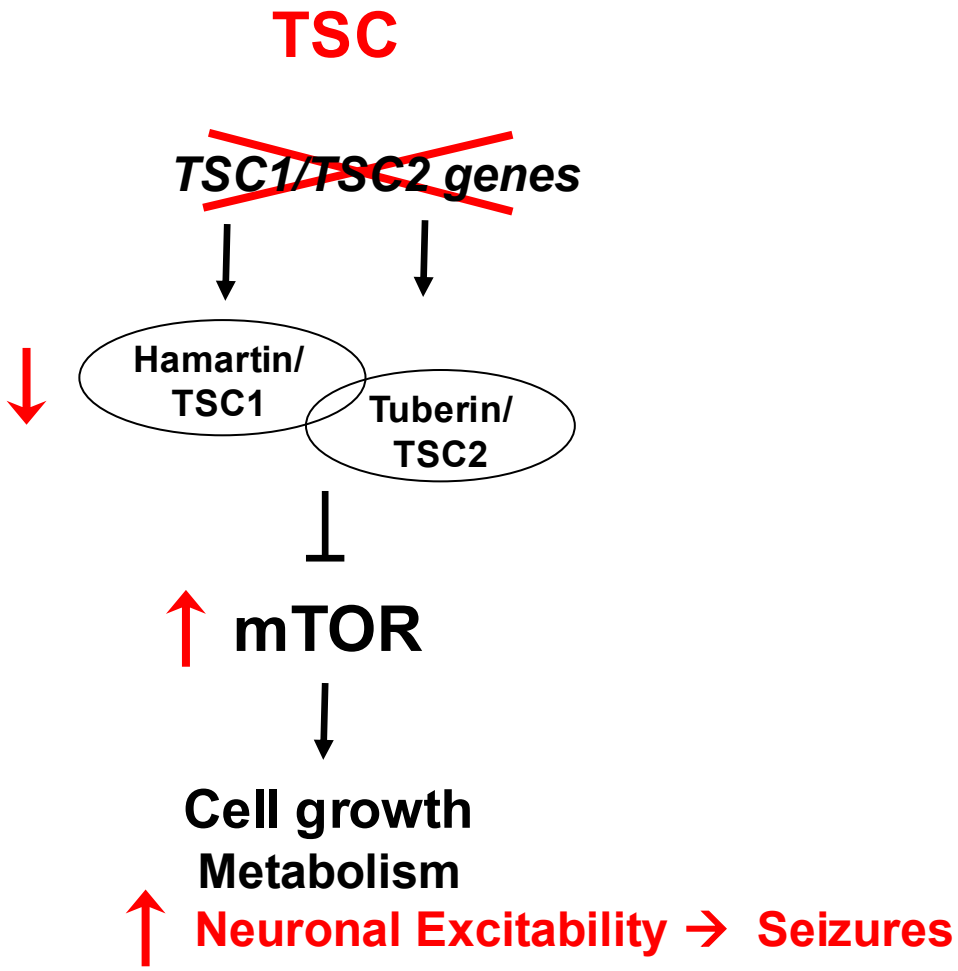
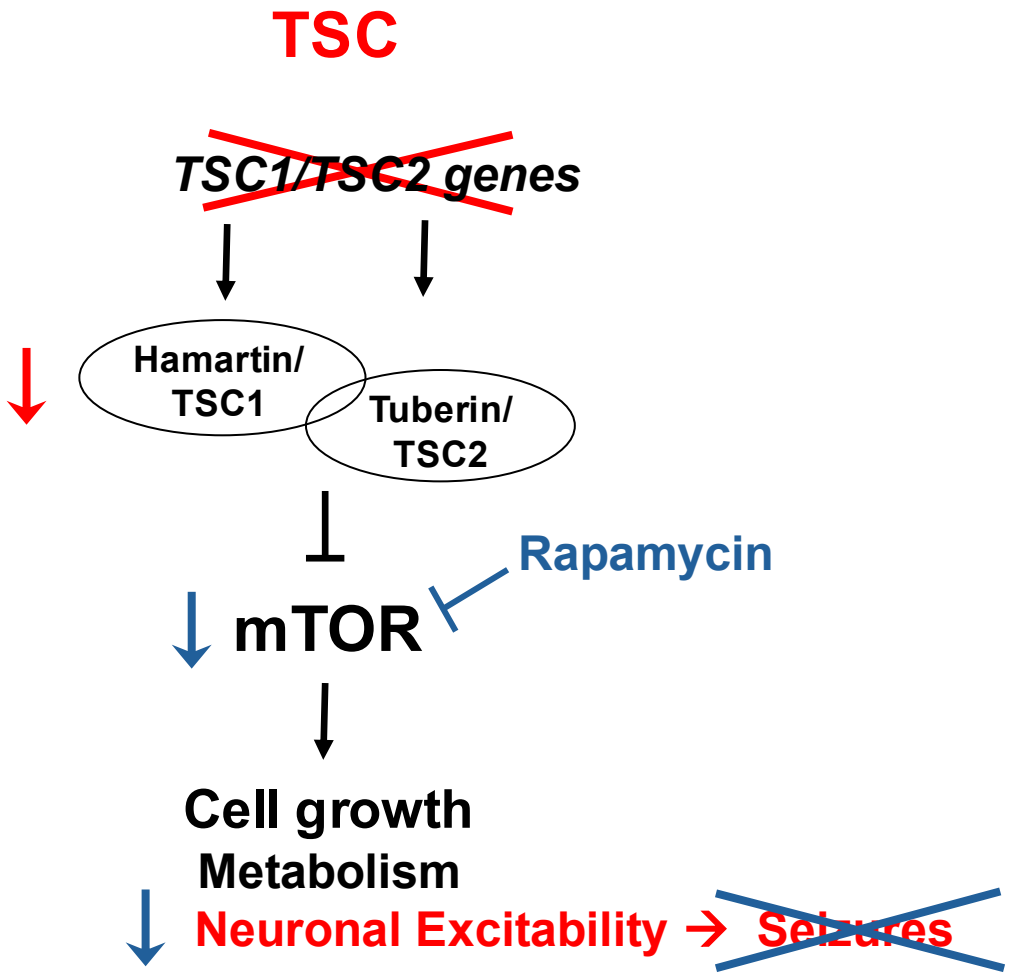
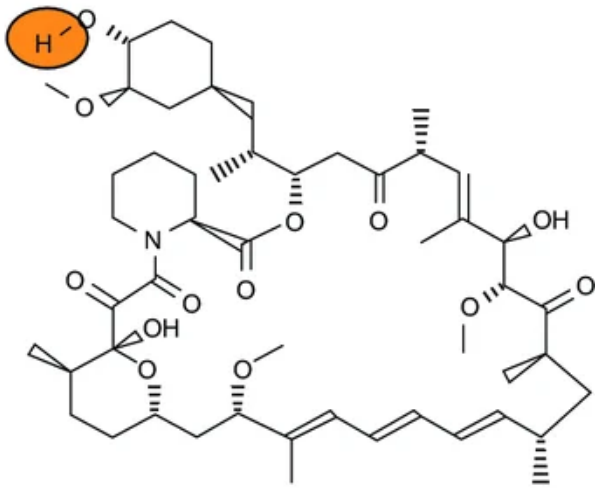


The TSC genes and the mTOR pathway

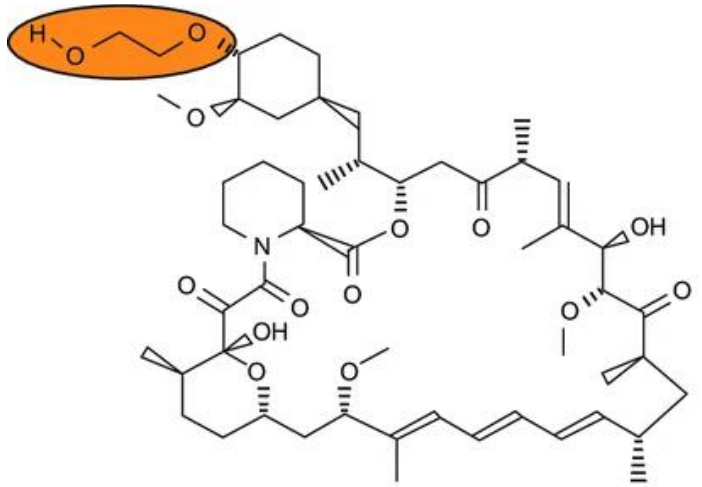


mTOR Inhibitors: Approved indications for TSC



Sirolimus/Rapamycin

Lymphangioleiomyomatosis (LAM)
Facial Angiofibromas (topical)



Everolimus/Affinitor

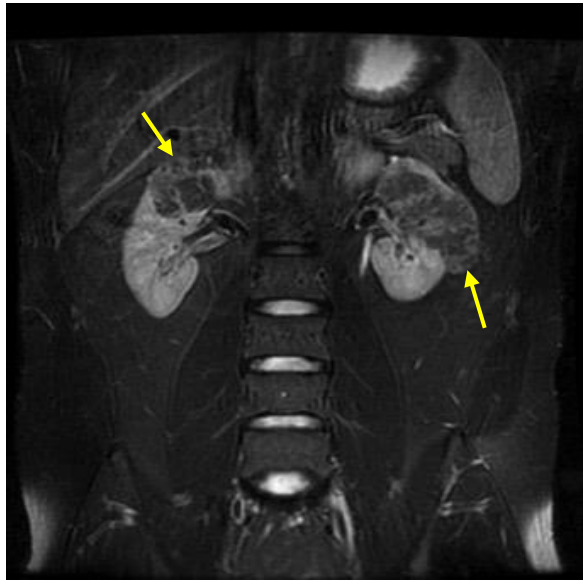
Subependymal Giant Cell Astrocytomas (SEGA)
Renal Angiomyolipomas
Intractable Epilepsy/Focal seizures

Present

Treatment of tumors in TSC with mTOR inhibitors

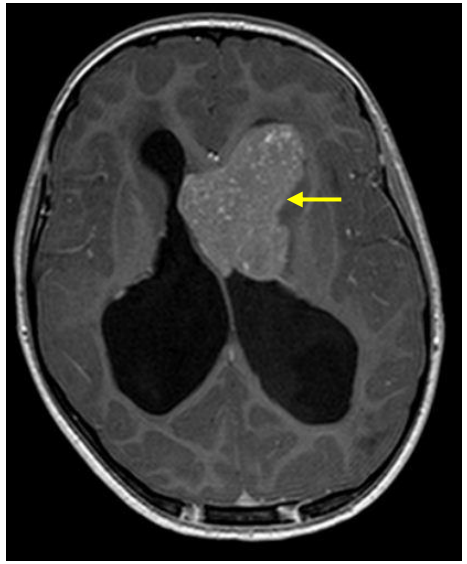
Tumors in TSC

- Tumors – overgrowth of cells in various organs is common in TSC
  - Kidney (angiomyolipomas, AMLs) occur in 50-80%
  - Skin (angiofibromas) occur in 50-90%
  - Brain (subependymal giant cell astrocytoma, SEGA) occur in 10-25%
  - Lung (lymphangioleimyomatosis, LAM) occur in 5-15%
  - Several other organs can have hamartomas/tumors (pancreas, eye, connective tissue, liver, etc)
- While most tumors are not cancerous or aggressive, they cause symptoms when large
- Treatment historically was with surgical procedures in symptomatic patients

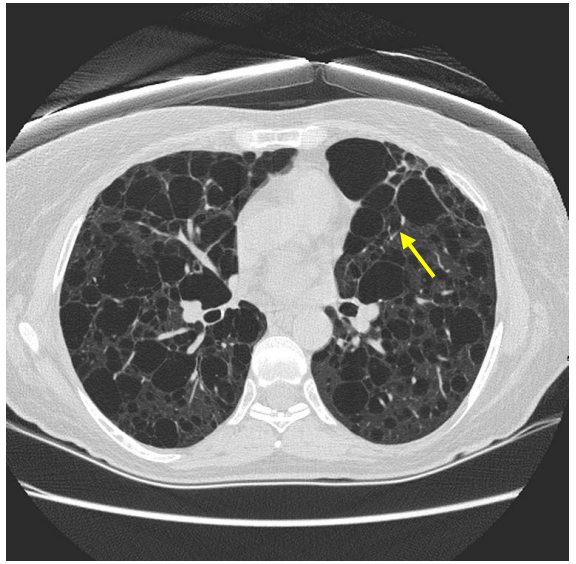


Kidney AML

Facial Angiofibroma

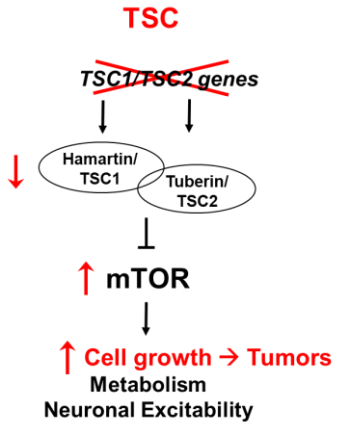


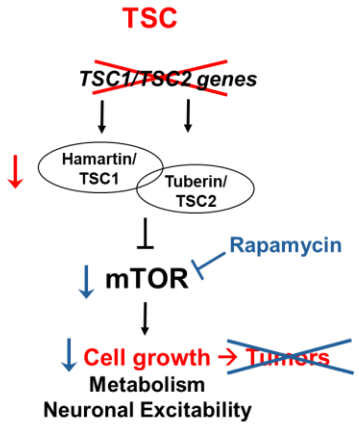
SEGA

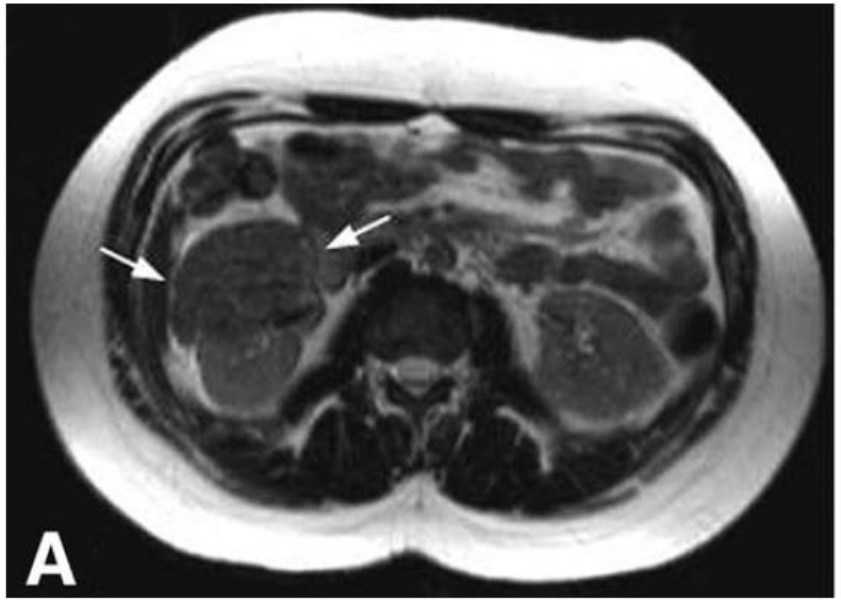


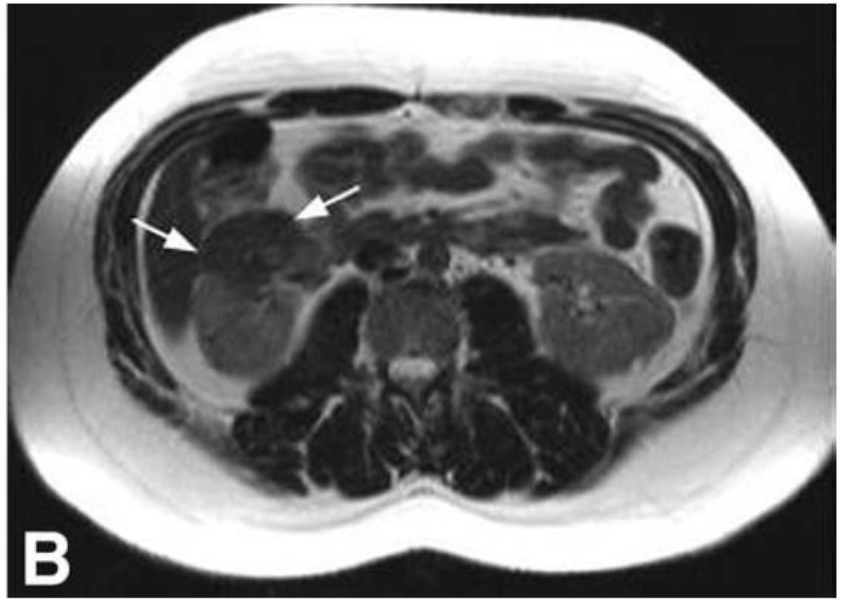
LAM

Initial Reports of mTOR inhibitors in TSC

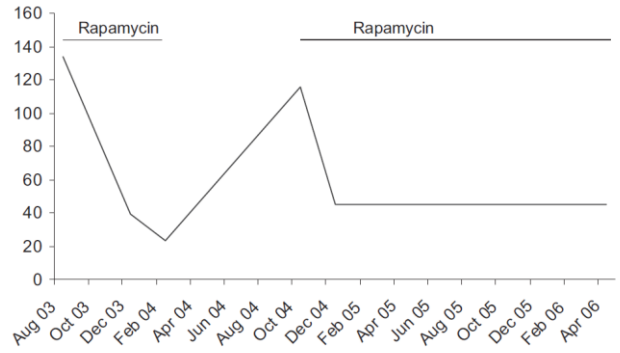






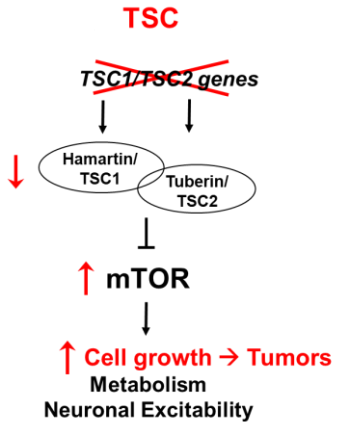


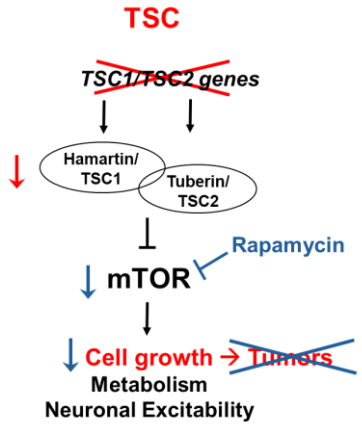
"Because animal trials of tuberous sclerosis showed an effect of rapamycin on renal tumors, our patient was administered rapamycin for 6 months."

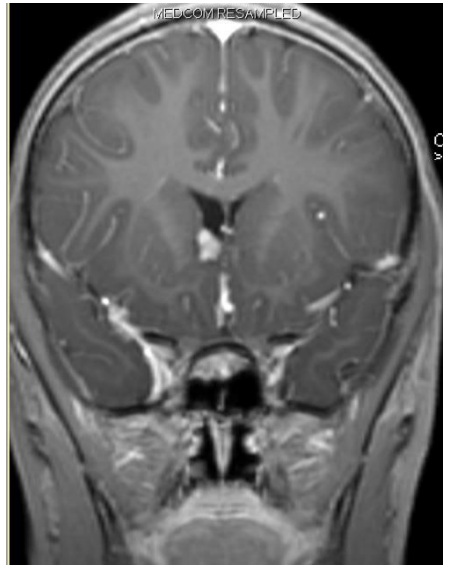


Wienecke et al. Am J Kidney Dis 2006

Initial Reports of mTOR inhibitors in TSC







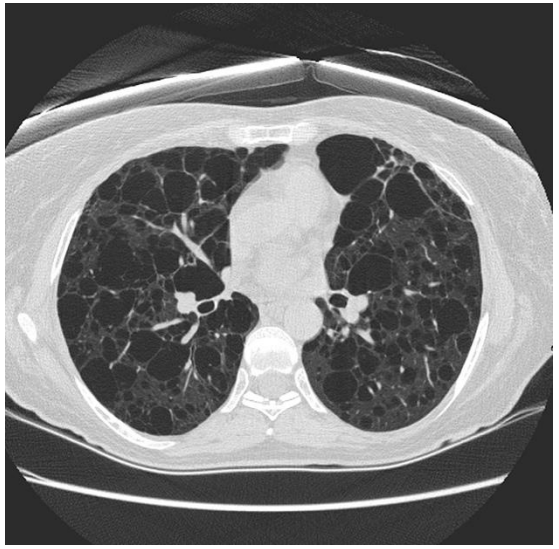
Franz et al. Ann Neurol, 2006

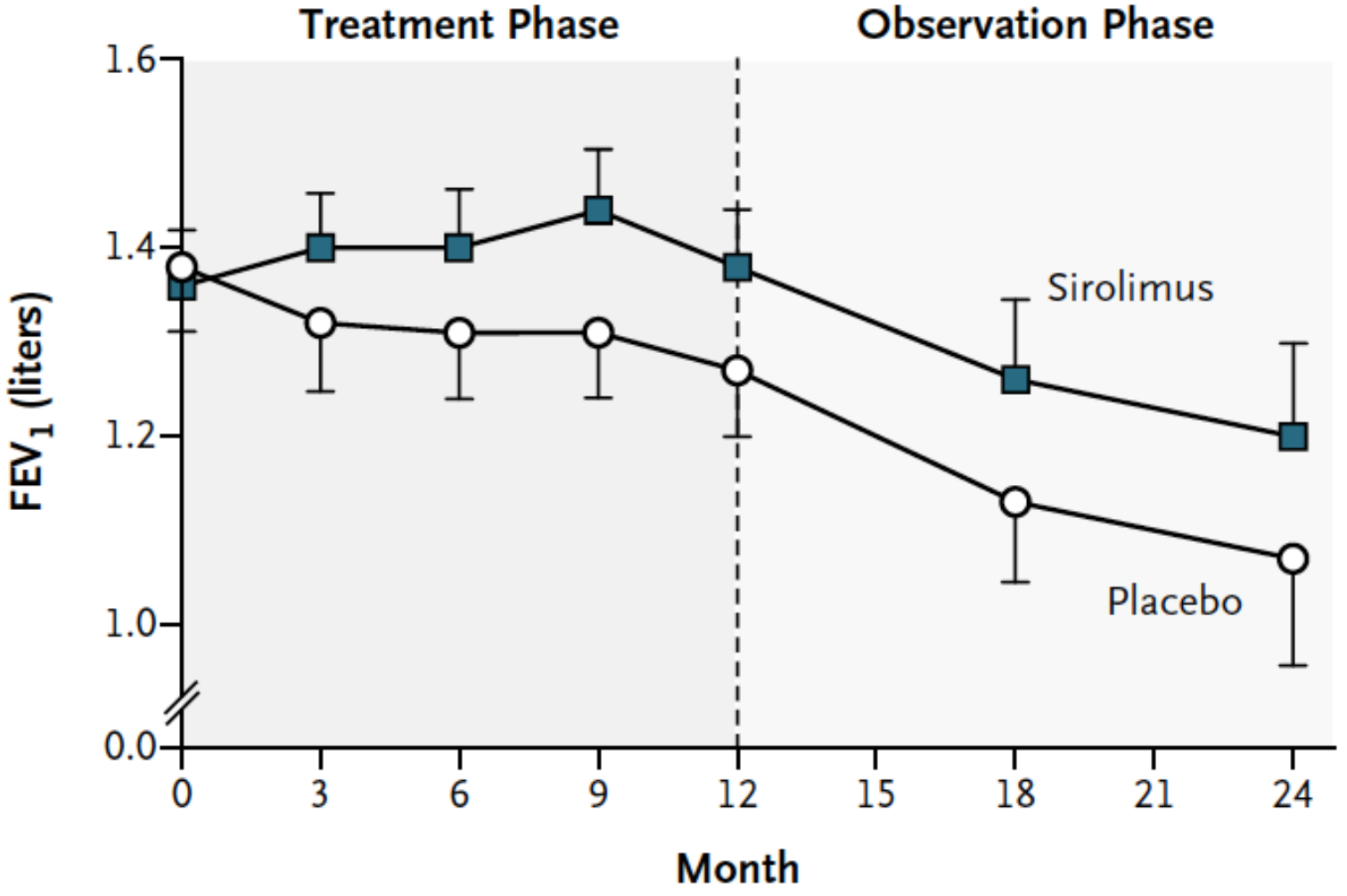
Table 2. Response of Primary Subependymal Giant-Cell Astrocytomas (SEGAs) to Everolimus Therapy at 6 Months, among the 28 Patients, According to Type of Assessment.*

SEGA Volume	Local Investigator's Assessment		Independent Central Review	
	Baseline	6 Mo	Baseline	6 Mo
Mean — cm^3	2.25±1.66	1.24±0.90	2.45±2.81	1.30±1.48
Median — cm^3	2.00	0.96	1.74	0.93
Range — cm^3	0.35–7.10	0.19–3.40	0.49–14.23	0.31–7.98
Reduction from baseline				
Mean — cm^3	1.01±1.04		1.15±1.42	
Median (95% CI) — cm^3	0.92 (0.5–1.4)		0.80 (0.4–1.2)	
P value	<0.001		<0.001	
Percent reduction — no. (%)				
≥50	11 (39)		9 (32)	
≥30	21 (75)		21 (75)	
>0	28 (100)		28 (100)	

Krueger et al. NEJM, 2010

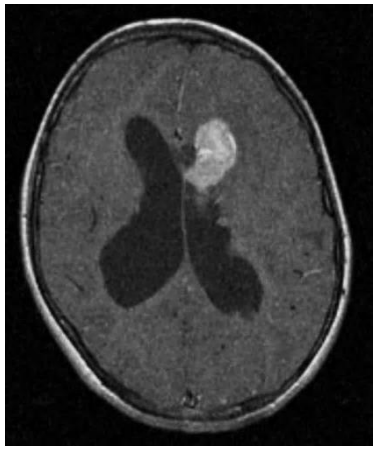
Sirolimus for LAM



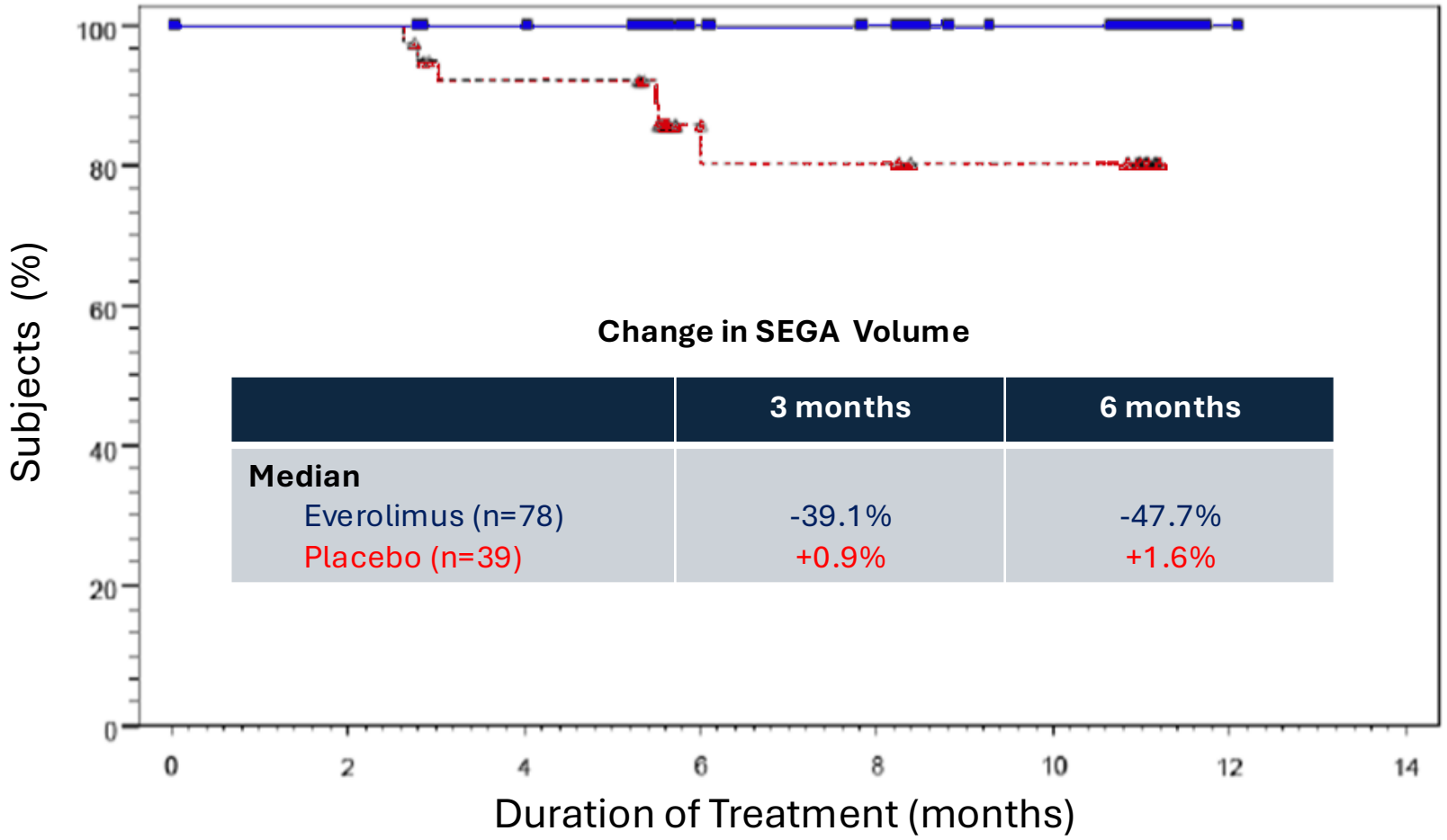


McCormack et al., NEJM 2011

Everolimus for SEGA



SEGA Progression

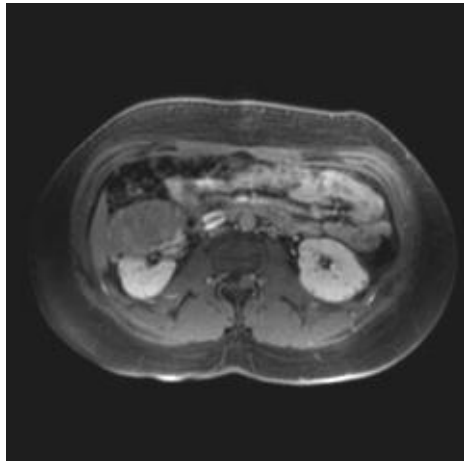


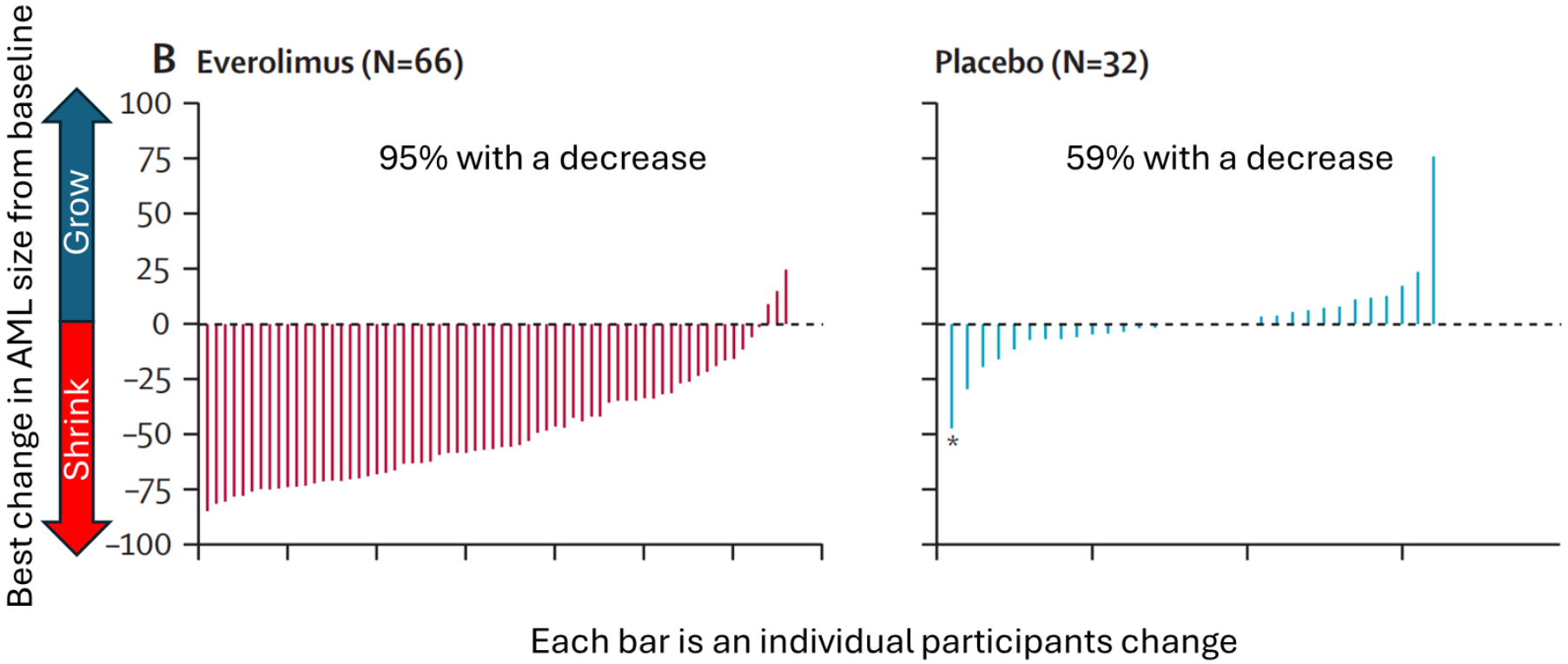
Change in SEGA Volume

	3 months	6 months
Median		
Everolimus (n=78)	-39.1%	-47.7%
Placebo (n=39)	+0.9%	+1.6%

Franz et al. *Lancet 2012*

Everolimus for AMLs



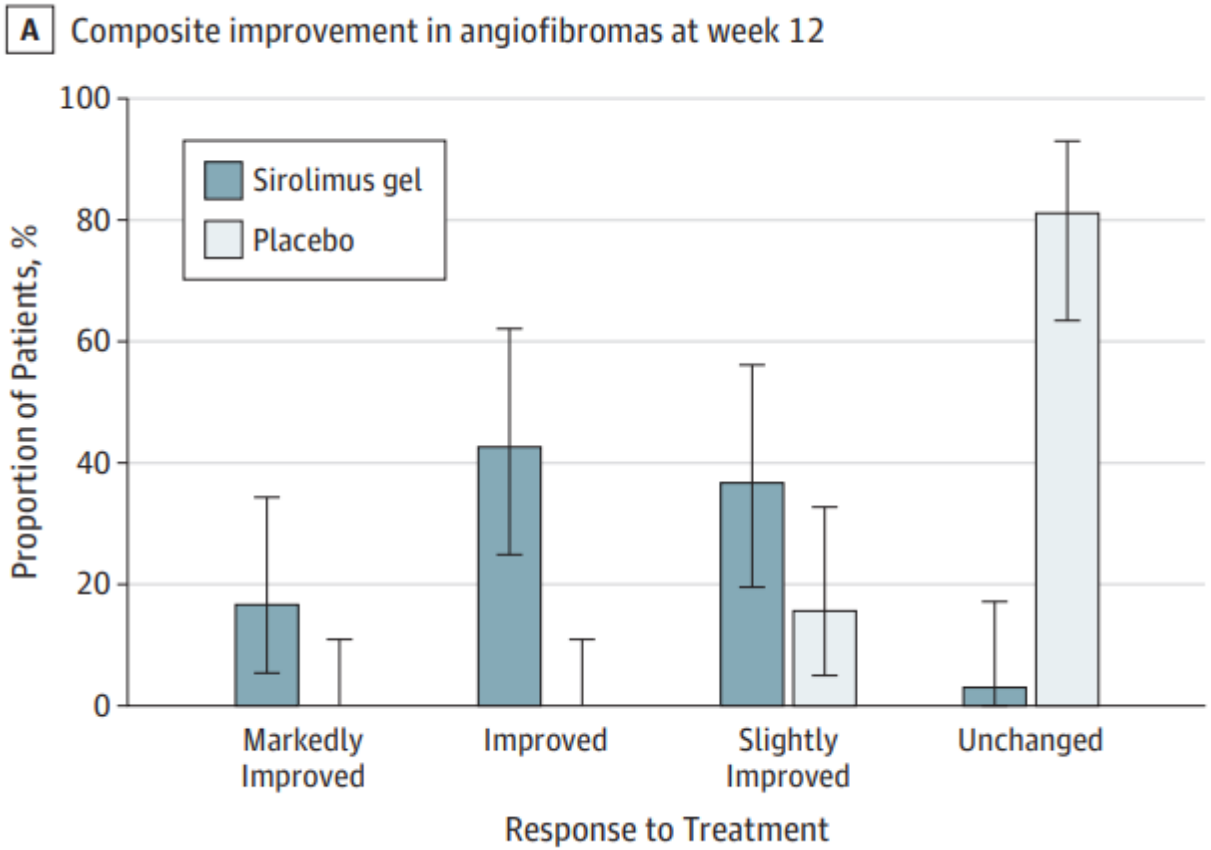


Bissler et al. *Lancet 2013*

Sirolimus for angiofibromas

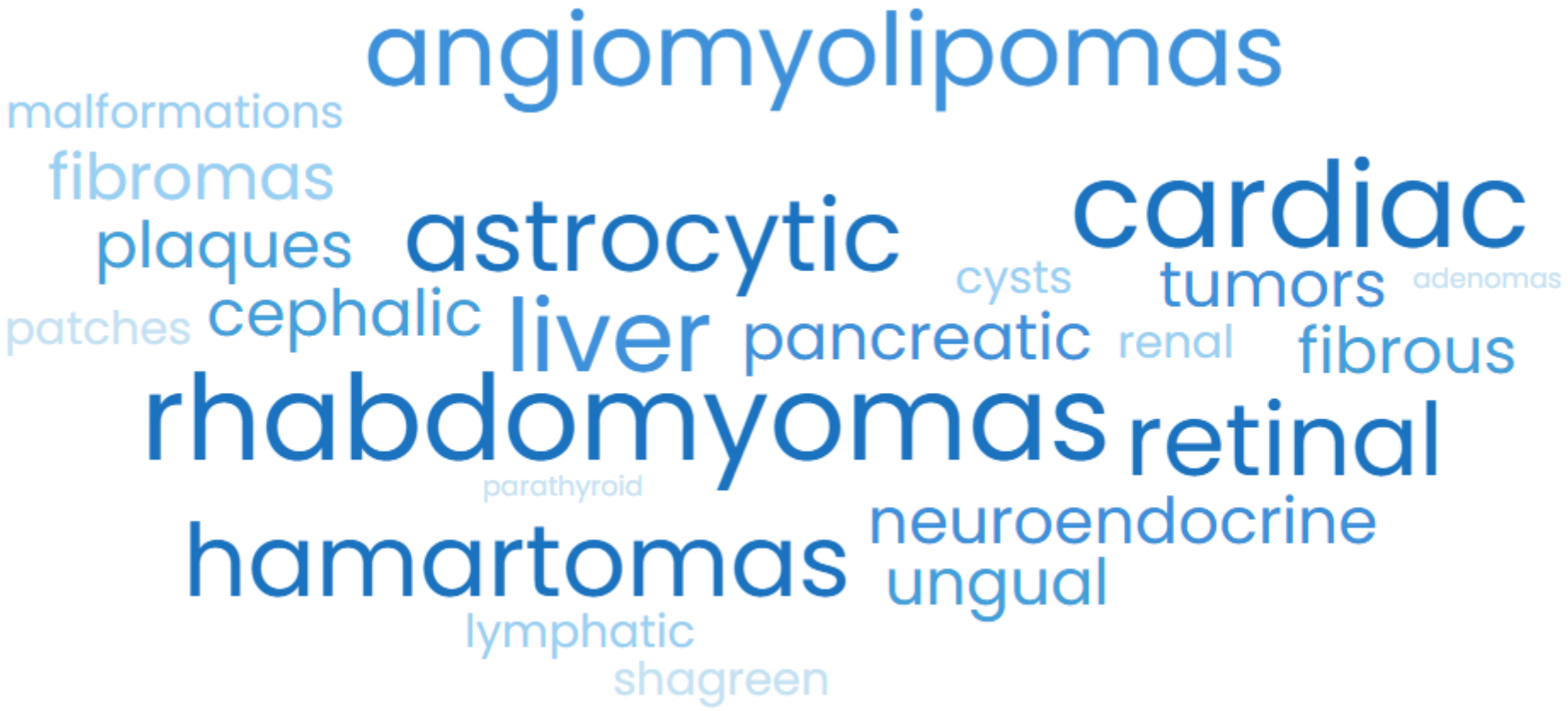
A Patient 1 baseline

E Patient 1 at 12 weeks



Wataya-Kaneda et al. *JAMA Derm 2018*

What other lesions respond?

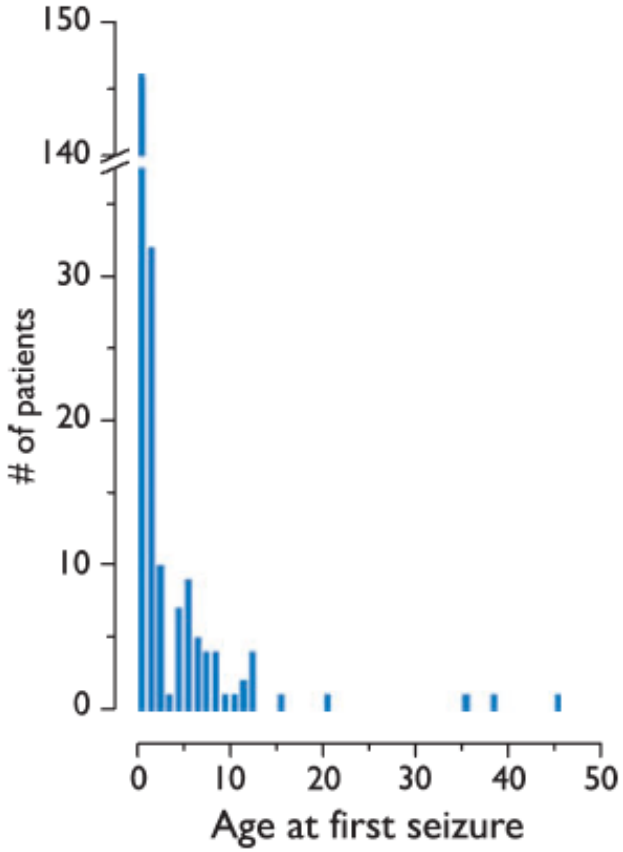


Present

Treatment of epilepsy and neurological symptoms in TSC with mTOR inhibitors

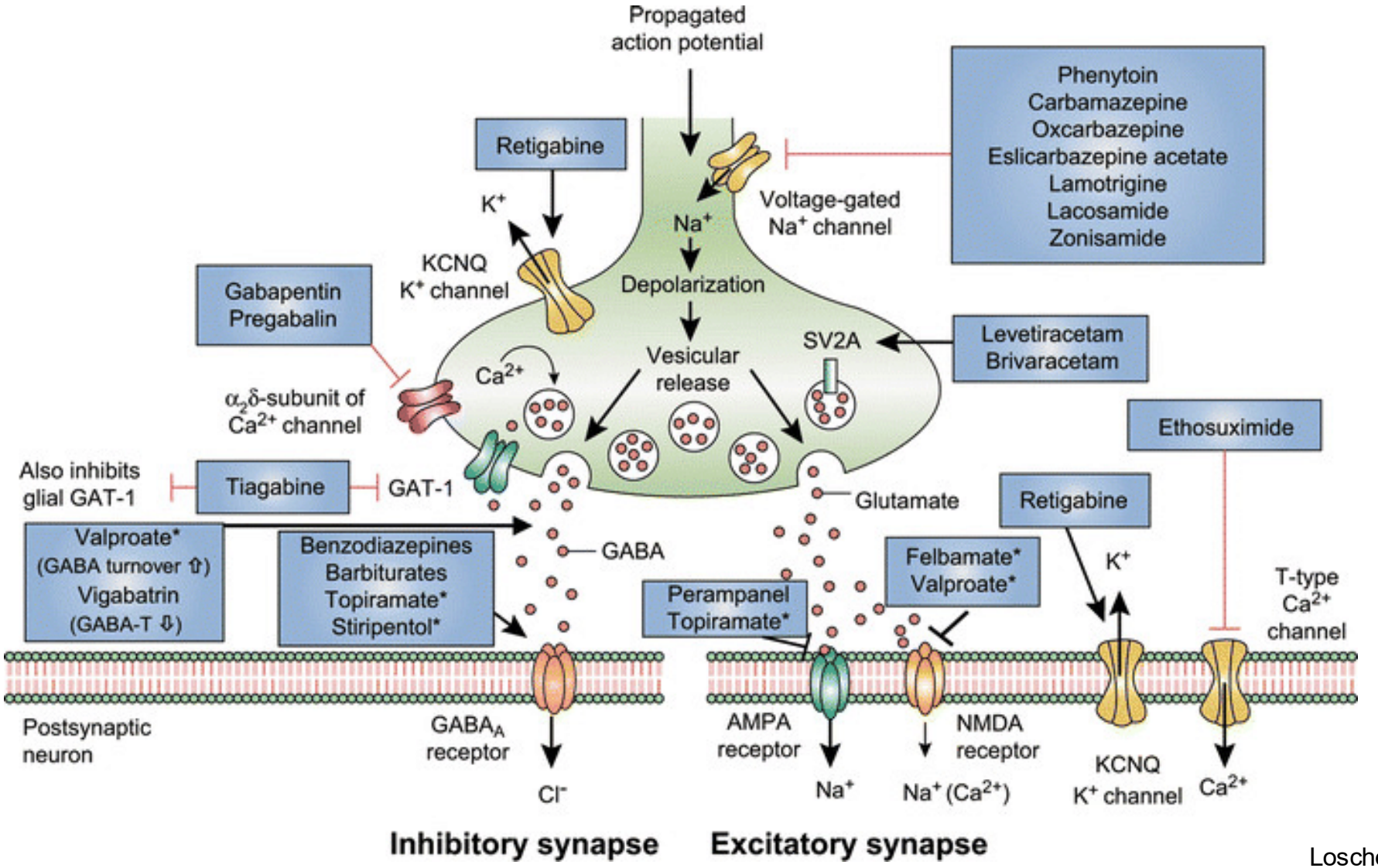
Epilepsy in TSC

- Epilepsy is very common in TSC, occurring in 80-90% of TSC patients.
- Age of seizure onset is <1 year in 63% and <3 years in 82% of TSC patients.
- Infantile spasms occur in about one-third of patients with TSC.
- Multiple seizure types occur in about a half of TSC patients, including focal seizures.
- ~70% of TSC patients with epilepsy are drug-resistant (exception: vigabatrin for spasms).
- Some TSC patients are candidates for epilepsy surgery (e.g. tuberectomy) and other non-medical options, but many TSC patients are still left with life-long intractable seizures despite all available treatments.



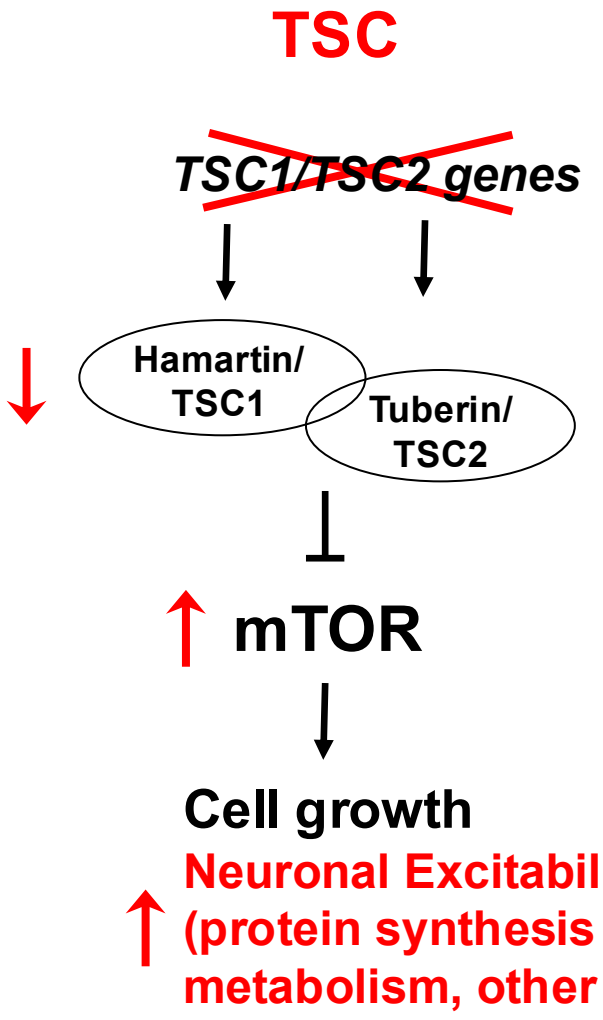
Chu-Shore et al. Epilepsia 2010

Mechanisms of Action of Antiseizure Medications



Loscher et al. CNS Drugs 2016

The mTOR pathway and epilepsy in TSC



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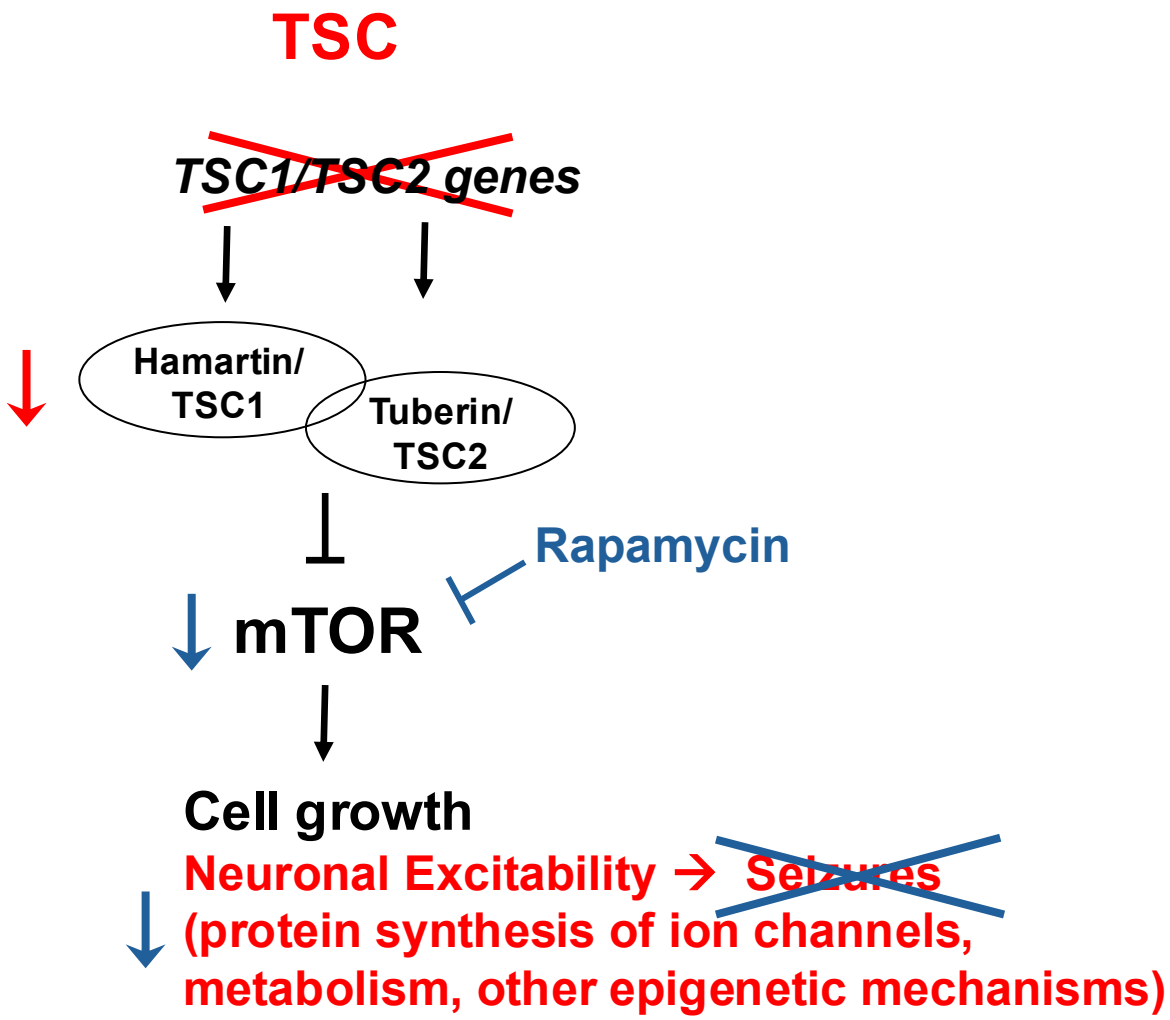
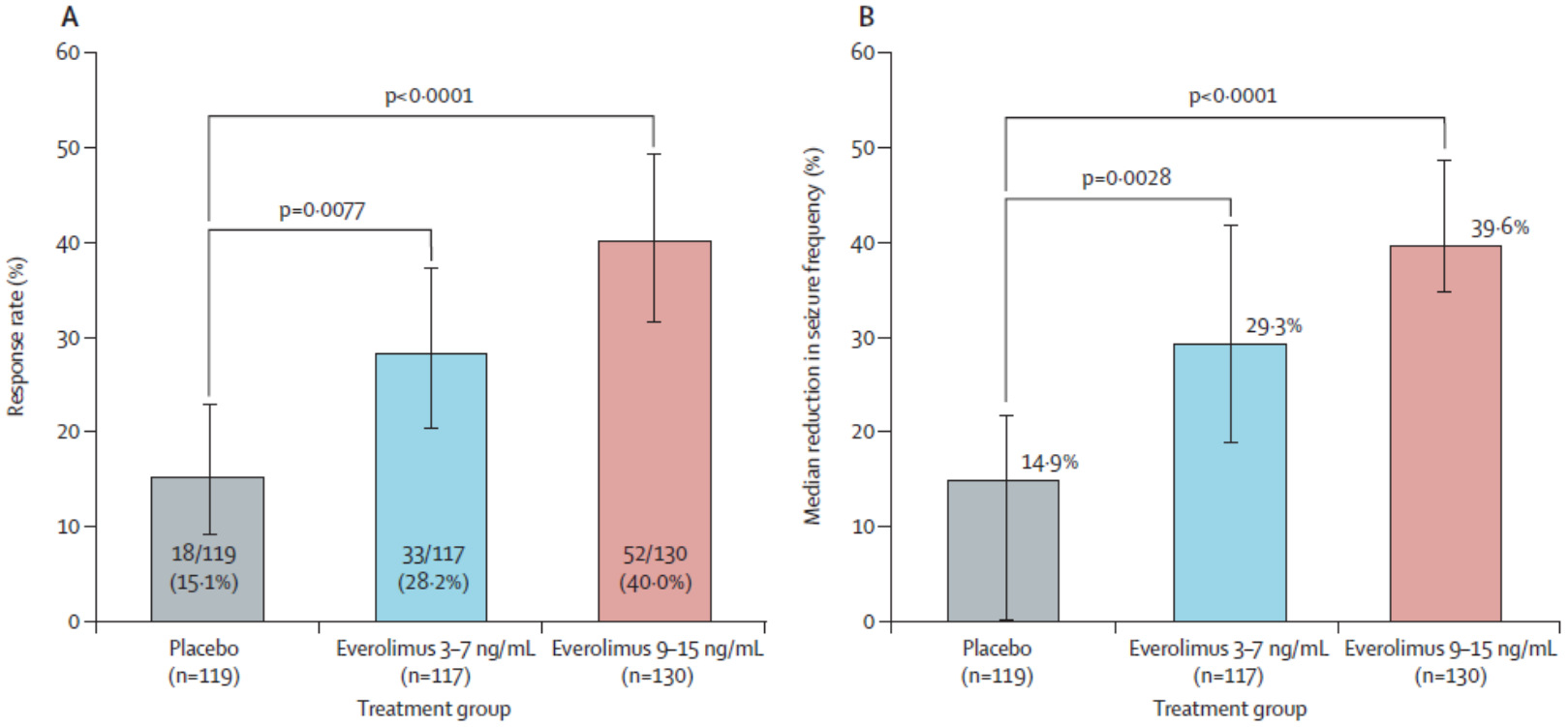


Clinical trials of everolimus for epilepsy in TSC

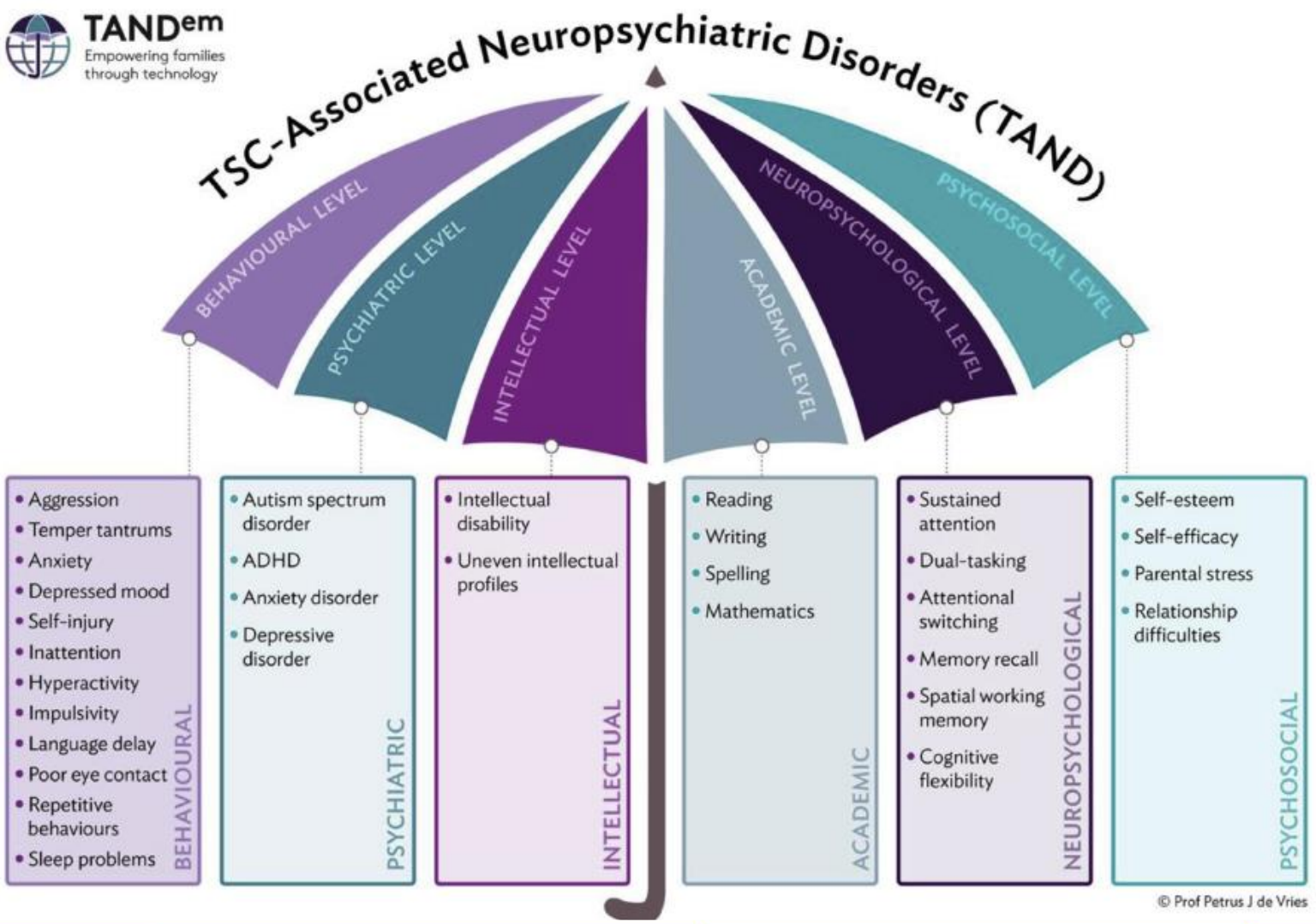
Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomised, double-blind, placebo-controlled study



French et al. Lancet 2017

mTOR inhibitors and TAND???

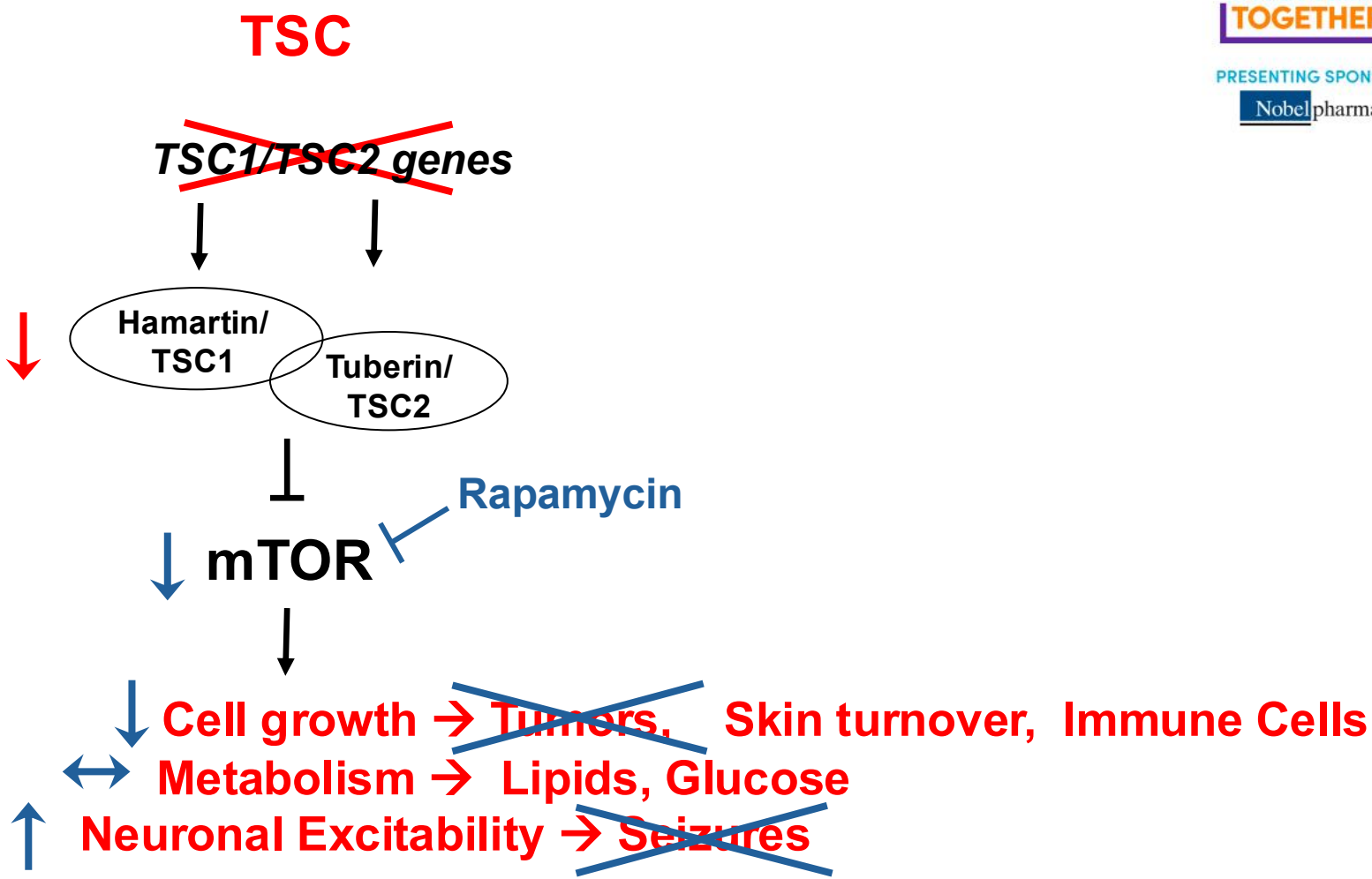
H. Northrup, M.E. Aronow, E.M. Bebin et al. Pediatric Neurology 123 (2021) 50–66



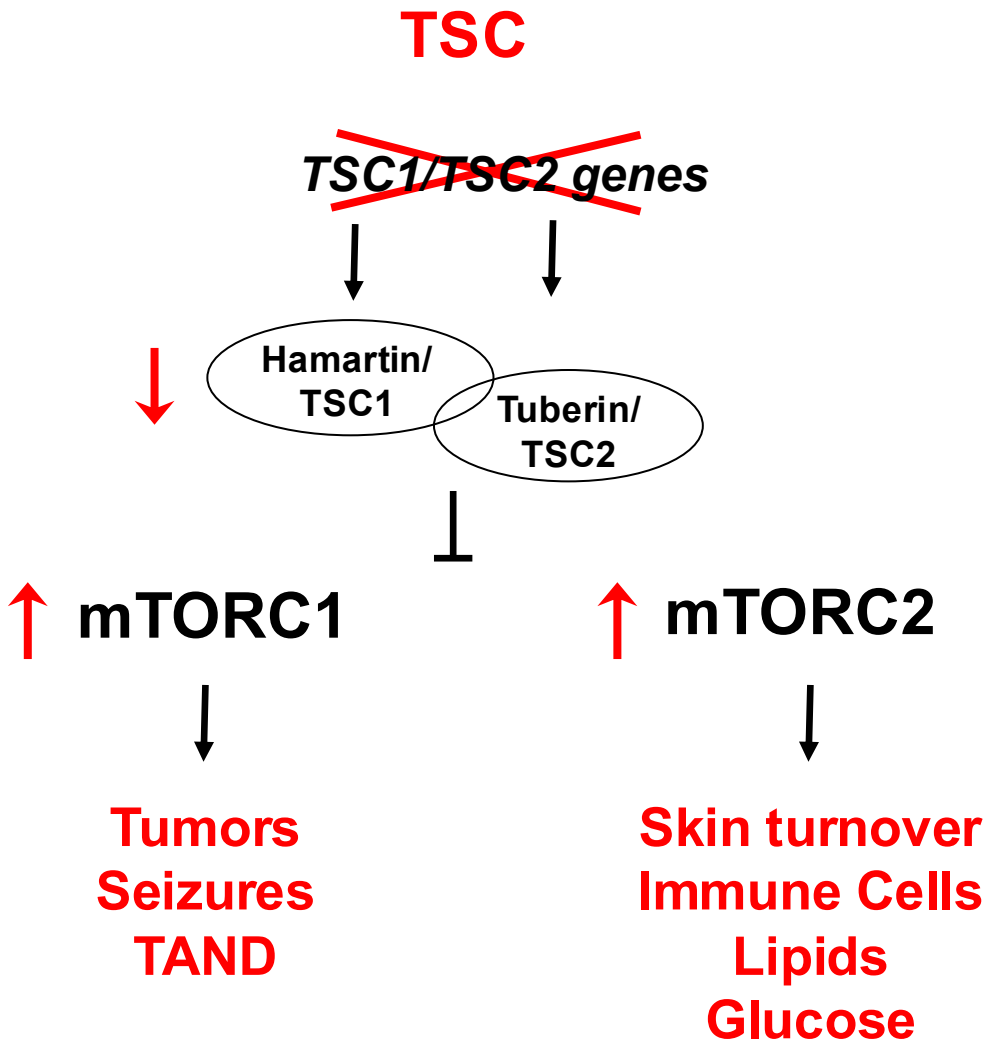
Present

Side effects of mTOR inhibitors

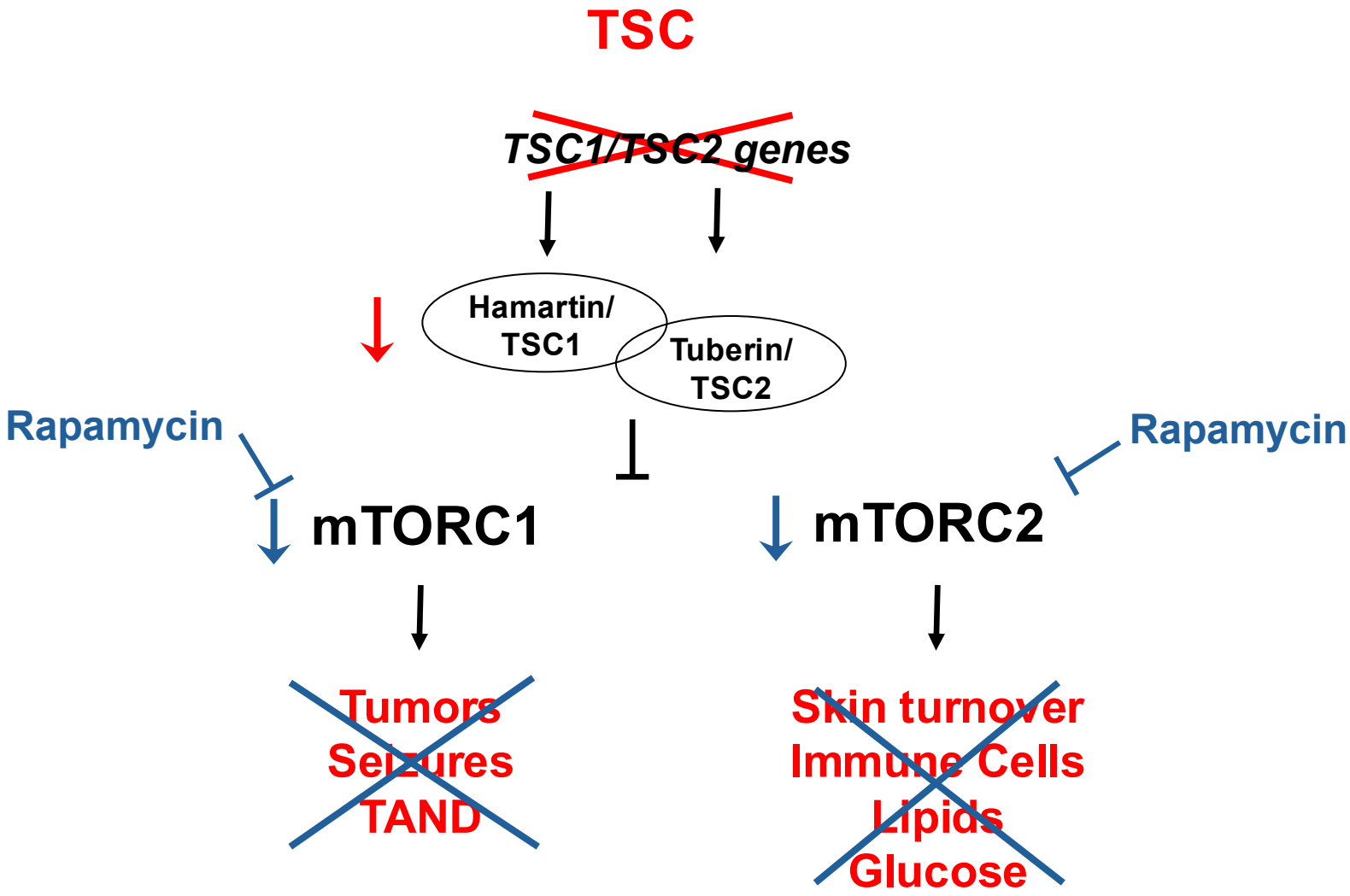
mTOR inhibitors and side effects



mTOR inhibitors and side effects



mTOR inhibitors and side effects



Common Side Effects in the EXIST Clinical Trials

	% Treated - Placebo *
Stomatitis	41%
Mouth Ulceration	19%
Any event#	14%
Diarrhea	12%
Fever	8%
Cough	6%
Fatigue	6%
Rash	5%
Pharyngitis	4%
Acne	4%
Vomiting	4%
URI	1%
Ear Infection	1%
Nasopharyngitis	-3%

*Average of the percent treated who reported the side effect – the average of the percent treated with placebo who reported the side effect

#This includes lab changes: including lipid elevations

Modified from Franz et al Clin Epileptology 2026

Practical guidelines

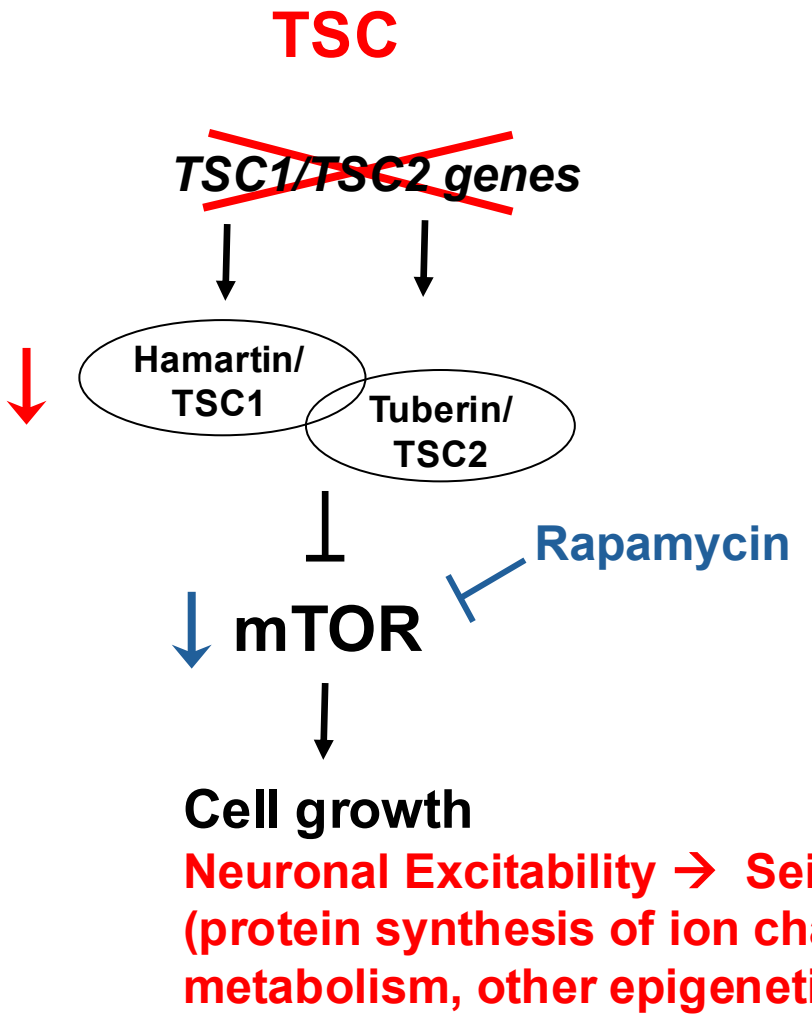
- **Mouth sores** – very common
  - Have a plan on how to treat them
  - Seems to get better over time with treatment
- **Infections** – most common concern
  - Have a sirolimus or everolimus plan for fevers and antibiotics
- **Lipids/Metabolic** – frequent problem
  - Monitor with lab testing, rarely have to treat
- **GI side effects** – most likely reason to stop early
  - Usually improves over time

Management depends on the provider – sometimes a dose adjustment or another medication to treat the side effect

Future

New treatment directions for mTOR inhibitors

The mTOR pathway and epilepsy in TSC

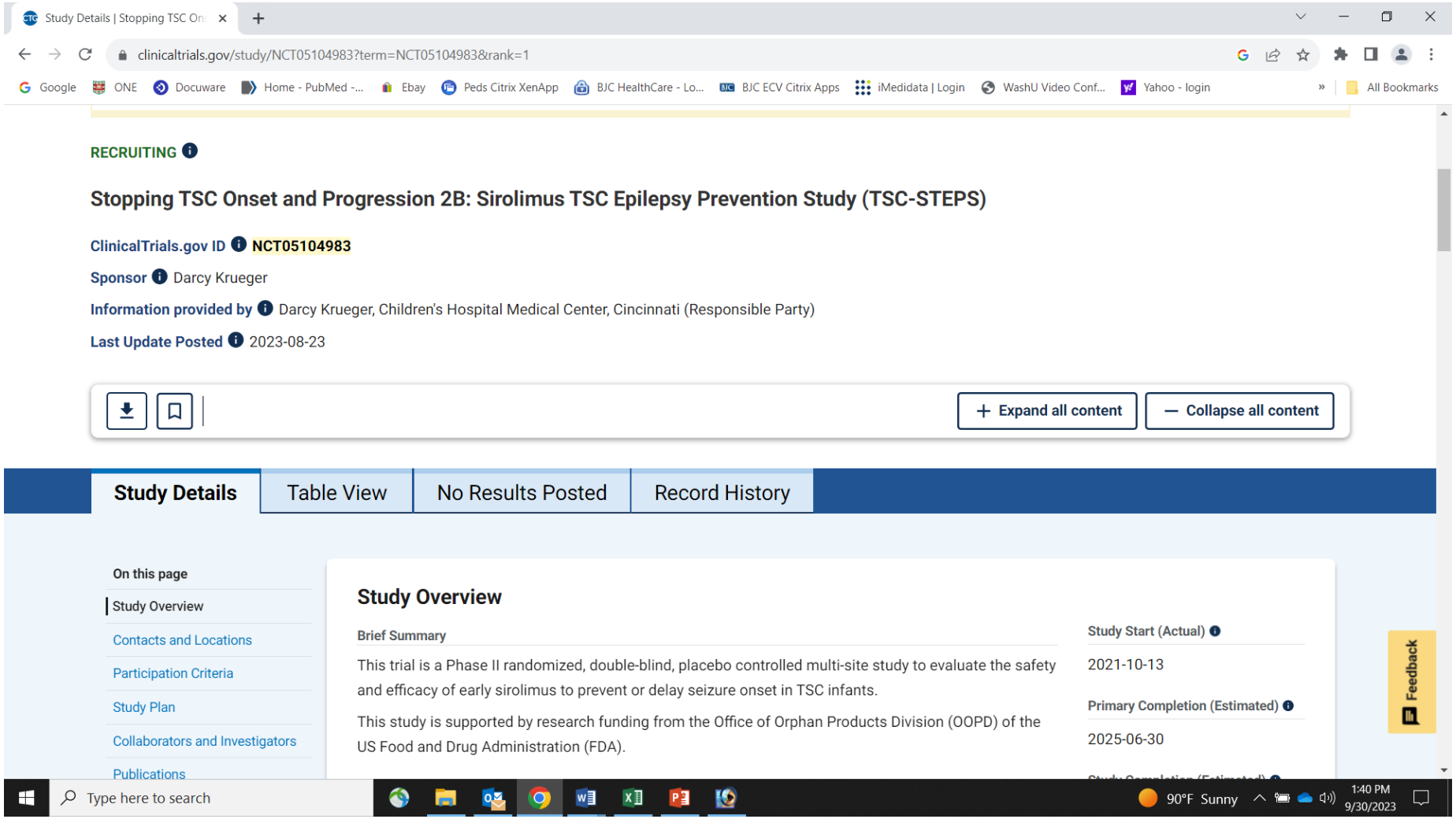


Preventative Treatment for Epilepsy in TSC?

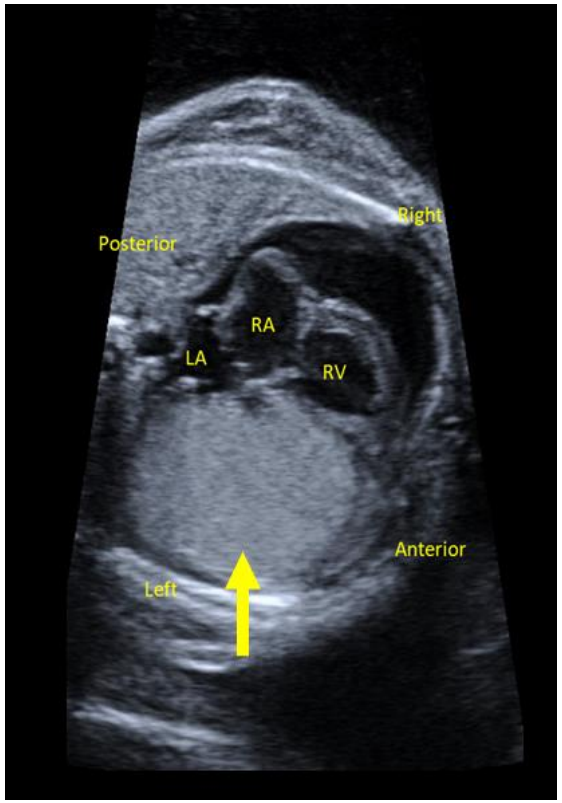
TSC as a model disease for developing a preventative therapy for epilepsy

- Presymptomatic patient identification (feasibility)
- High risk population (~80-90% will develop epilepsy) (justifiability)
- Rational drug target (mTOR) for epileptogenesis

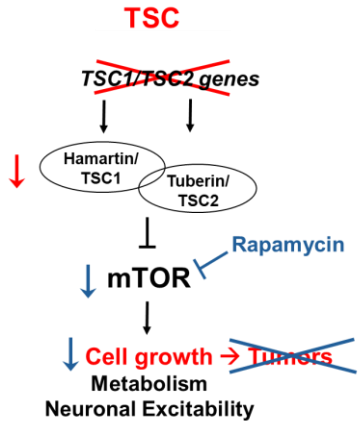
Preventative Treatment for Epilepsy in TSC?



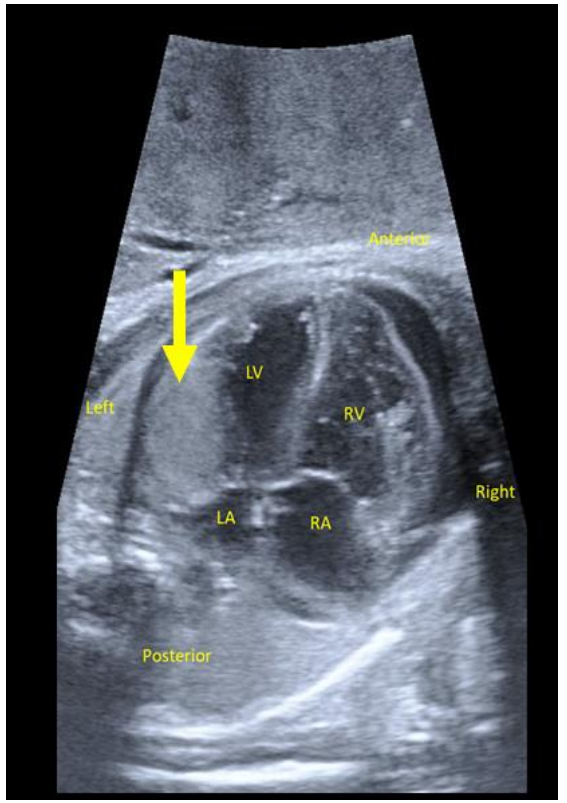
Prenatal Treatment of Cardiac Rhabdomyomas



26 weeks gestation



Mother prescribed sirolimus to take orally. It crosses the placenta and gets into the fetal blood.



34 weeks gestation

Preventative Prenatal Treatment?

Fetal TSC

Birth

TSC Disease at 1 year

Final TSC Disease State

Risk factors for Neurodevelopmental Complications

Timing of current interventions

TSC Mutation

Aberrant brain development & tubers

Maternal/fetal complications

Epileptiform discharges

Seizures

Life Experiences/Exposures

Sirolimus trials

Vigabatrin

Antiseizure medications

Behavior/Psychiatric Medications/Tumor Treatment

What does it look like to treat here?

New directions for mTOR inhibitors

1) Temsirolimus and nab-sirolimus– IV formulations that can be given less frequently in cancer regimens *

2) Can you target mTORC1 only to reduce side effects?

3) Can you develop molecules that block mTOR inhibitor activity selectively, so it only works in a desired tissue?

4) What is the lowest effective dose of our current mTOR inhibitors?

*Not studied in TSC

Questions

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